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31. (Amended) A composition comprising the fusion protein of claim 26 and diluent, said composition being free of contamination by other clostridial proteins.

REMARKS

Reconsideration is requested. Claims 3-28 and 30-33 are pending. Claims 13-18 and 25 have been withdrawn from consideration. Claims 3, 4, 20, 22, 23, 24 and 27 have been canceled, without prejudice, to advance prosecution. Accordingly, upon entry of the above amendments, claims 5-19, 21, 25, 26 and 28-33 will be pending. Entry of the above amendments will, at a minimum, reduce the issues for any possible appeal, for the reasons described below. Entry of the above amendments therefore is requested.

The present Second Amendment presents the same amendments and remarks as the Amendment filed September 5, 2001, with additional amendments to claim 8 to include an "and" to recite a more traditional Markush group, and to amend claims 13-18 and 25 to be dependent on what the applicants submit are allowable protein claims and in support of the attached Request for Reconsideration of the PETITION DECISION. The following additional comments are also similarly presented in the attached Request and are included herein for completeness.

Reconsideration and withdrawal of the restriction requirement is again requested. The applicants traversed the restriction requirement and requested reconsideration of the same in their response of September 14, 1999. The restriction requirement was maintained in the Examiner's Action of October 7, 1999. The applicants filed a Petition

under Rule 181 on January 7, 2000, for the Commissioner to invoke his supervisory authority to have the restriction requirement withdrawn. The applicants requested, in the interest of efficient prosecution, consideration of the Petition prior to further action on the merits. Contrary to the applicants request, a further Action on the merits was issued March 16, 2000. A reply to the Action of March 16, 2000, was filed June 16, 2000, which included a request for a Decision on the Petition. A supplemental amendment was filed June 19, 2000. A Status Request was filed December 19, 2000. A Notice to Comply was mailed February 27, 2001, and a Response to the Notice to Comply was filed March 27, 2001. A further Action on the merits, which is a final rejection, was mailed June 5, 2001. The Examiner acknowledged the Petition in the final Office Action and advised the applicants to contact the Examiner or Mr. Kunz if a Decision was not received **"in a timely fashion"**. A Decision on the applicants' Petition filed January 7, 2000, was mailed August 10, 2001, i.e., 18 months after filing the Petition and after the issuance of three further papers and a final rejection by the Patent Office. The Decision denied the applicants' Petition, and set a two-month period for requesting reconsideration. The present Amendment is being filed in support of the attached Request for Reconsideration.

The undersigned submits, with all due respect, that the failure of the Patent Office to timely respond to the applicants' Petition of January 7, 2000, has been prejudicial to the applicants as, at least, the applicants must now pay for a one month extension to amend the claims in support of the attached Request for Reconsideration. Had the Patent Office mailed a Decision on the Petition prior to issuance of the final

rejection, the applicants would not have been required to pay for further extensions to further amend the claims. A Refund Request is therefore attached requesting refund of the attached one month extension fee.

The applicants submit that, pursuant to Rule 116(c), the above amendments, at least with regard to claims 13, 14 and 17, are necessary to place claims 13-18 and 25 in condition for allowance and in condition to define a special technical feature in common with the remaining claims which are under active consideration. Moreover, the amendments were not previously made as the amendments have been made in response to the Petition Decision dated August 10, 2001 and in support of the attached Request for Reconsideration. Entry of the amendments is requested and submitted to comply with the requirements of Rule 116(c).

In the event the above amendments are not entered, withdrawal of the finality of the Office Action of June 5, 2001 is requested as the applicants Petition of January 7, 2000, had not yet been decided prior to issuance of the final rejection. Accordingly, issues relating to the merits of the patentability of the claims and the scope of the patentably distinct inventions, according to the U.S. Patent Office's interpretation of the requirements for Unity of Invention, were outstanding when the final Office Action was mailed on June 5, 2001.

Withdrawal of the restriction requirement is requested as, upon entry of the above amendments, the pending claims define a single invention.

That is, the Decision asserts that the holding of Lack of Unity is based on the

> "... evidence that the polypeptide is known and thus does not make a contribution over the art. As evidence that the polypeptide does

> not make a contribution over the art, the article in Current Microbiology [East et al., Current Microbiology 29, 69-77 (1994)] is initially cited." See, page 3 of the Petition Decision.

At the time the Decision was mailed by the Patent Office however, the Examiner had indicated that the claims of the elected polypeptide defined patentably over the "Current Microbiology" reference. The Examiner continued to reject however certain of the claims defining the subject matter of the elected polypeptide as allegedly being anticipated by Thompson (FEMS Microbiol Letters, 108: 175-82 (1993); claims 1-4, 7-10, 12, 19-24, 26-27 and 30-33), Simon (U.S. Patent No. 5,178,859; claims1-4, 7-12, 19-24, 26-27 and 30-33) and Sesardic (WO 94/21684; claims 3, 4, 7-10, 12, 19-24, 26-27, and 30-33). The applicants' Amendment of September 5, 2001, the substance of which is repeated herein because as the applicants have not yet received a response to the same, place the polypeptide claims in condition for allowance over the cited art, for the reasons described below. That is, upon entry of the above amendments, the polypeptides of the claimed invention make a contribution over the art.

The Decision states that:

> "... PCT Rules allow review of any Unity or Lack of Unity holding at each stage of prosecution. The determination may, therefore, change with each Office action depending on the prior art discovered and the applicant's actions. Such is no different from restriction practice in regularly filed applications where the examiner reviews the restriction requirement for correctness with each Office action." See, page 3 of the Decision.

Accordingly, it is the applicants understanding that the basis of the restriction requirement was a belief by the Examiner, and the Director of Technology Center 1600 (i.e., Jasemine C. Chambers), that the restriction requirement was proper between the

polypeptides and the DNA encoding the polypeptide because the elected subject matter (i.e., polypeptides), **as defined by the claims pending at the time of the restriction requirement**, allegedly failed to make a contribution over the prior art. It is also the applicants understanding that the "correctness" of the restriction requirement is reviewed "with each Office action". [1]

The claims of the elected Group have been amended above to define over the art, as described below. The elected polypeptides, as defined in the claims, are therefore submitted to define a special technical feature in common with the subject matter of the Examiner's Group II (i.e., DNA encoding the polypeptides). The non-elected claims have been similarly amended, to advance prosecution. The Examiner is requested therefore to enter the above amendments, review the restriction requirement for correctness, withdraw the restriction requirement and consider all of the claimed subject matter on the merits.

The following remarks are, as described above, re-presented for completeness.

The Section 112, first paragraph, rejection of claims 22-24 will be moot upon entry of the above amendments. Accordingly, entry of the above amendments will reduce the issues for any possible appeal by making the Section 112, first paragraph, rejection of claims 22-24 moot.

The Section 102 rejection of claims 3, 4, 7-10, 12, 19-24, 26-27, and 30-33 over Sesardic (WO 94/21684) as evidenced by Sigma Catalog 1992, pages 1585 and 1592-

[1] Clarification is requested in the event that the applicants have not understood the Patent Office position stated in the Decision.

93, is obviated by the above amendments. Specifically, the claims have been amended, to advance prosecution, to be based on claims 5 and 6, for example, which have been found to be novel over Sesardic. Entry of the above and withdrawal of the Section 102 rejection of the recited claims over Sesardic is requested.

Similarly, the Section 102 rejection of claims 1-4, 7-12, 19-24, 26-27 and 30-33 over Simon (U.S. Patent No. 5,178,859) will be obviated upon entry of the above amendments. The applicants note the Examiner has rejected claims 1 and 2 however the same is no longer pending. Entry of the above and withdrawal of the Section 102 rejection are requested.

The objection to claim 8 is obviated by the above which deletes the objected-to phrase.

The Section 102 rejection of claims 1-4, 7-10, 12, 19-24, 26-27 and 30-33 over Thompson (FEMS Microbiol. Letters, 108:175-82, (1993)) is obviated by the above amendments which, as noted above, have been made to advance prosecution by canceling claims 3 and 4 and to recite the subject matter of claims 5 and 6, for example, which the Examiner has found novel over Thompson. Again, the Examiner has rejected claims 1 and 2, which were canceled in the Amendment of June 16, 2000. Withdrawal of the Section 102 rejection of the recited claims over Thompson is requested.

The Section 112, second paragraph, rejection of claims 3-12, 19-24, 26-28 and 30-33 is obviated by the above. The claims have been amended, to advance prosecution, for clarity and to obviate the Section 112, second paragraph, rejection with regard to the Examiner's concerns relating to functional recitations of the unamended

claims. Withdrawal of the Section 112, second paragraph, rejection of claims 3-12, 19-24, 26-28 and 30-33 is requested.

The Section 112, second paragraph, rejection of claims 26-28 and 30-31 is obviated by the above. The claims have been amended, to advance prosecution, by canceling claim 27 which contains the language objected to by the Examiner. Withdrawal of the Section 112, second paragraph, rejection of claims 26-28 and 30-31 is requested.

In view of the above and attached, all of the pending claims are submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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MARKED UP CLAIMS

5. (Four Times Amended) An isolated polypeptide [according to Claim 3 wherein said fragment is] comprising a sequence of amino acids selected from the group consisting of:

(a) amino acids 848-1278 of a type F botulinum toxin (SEQ ID NO: 1)

(b) amino acids 848-991 of a type F botulinum toxin (SEQ ID NO: 2)

(c) amino acids 992-1135 of a type F botulinum toxin (SEQ ID NO: 3), and;

(d) amino acids 1136-1278 of a type F botulinum toxin (SEQ ID NO: 4)

6. (Four Times Amended) An isolated polypeptide [according to Claim 3 wherein said derivative comprises] comprising a dimer of the [fragment] sequences selected from the group consisting of:

(a) amino acids 848-1278 of a type F botulinum toxin (SEQ ID NO: 1)

(b) amino acids 848-991 of a type F botulinum toxin (SEQ ID NO: 2)

(c) amino acids 992-1135 of a type F botulinum toxin (SEQ ID NO: 3), and

(d) amino acids 1136-1278 of a type F botulinum toxin (SEQ ID NO: 4)

7. (Four Times Amended) A polypeptide composition comprising:

(1) an isolated polypeptide according to claim [3] 5; and

(2) an isolated polypeptide that facilitates or enhances purification of the composition.

8. (Three Times Amended) A polypeptide composition comprising an isolated fusion protein of [(1)] a sequence of amino acids [corresponding to a fragment or a derivative of a heavy chain of a type F botulinum neurotoxin, which polypeptide is (a) free of botulinum toxin activity, (b) is free of toxoid, and (c) elicits, in a mammal, an immunological response that it protective against type F botulinum toxin, and (2)] selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, and SEQ ID NO:4, fused to a polypeptide that facilitates or enhances purification of the composition.

12. (Three Times Amended) A vaccine comprising a pharmaceutically acceptable carrier and a polypeptide according to claim [3] 5.

13. (Amended) A recombinant DNA encoding a polypeptide according to claim [3] 5.

14. (Amended) A method of producing a polypeptide according to claim [3] 5 comprising the steps of:

(a) expressing in a host cell a DNA encoding a fusion protein, said protein being a fusion of (i) a fragment or derivative of a type F botulinum toxin, and (ii) a moiety adapted to bind to a chromatography column,

(b) obtaining from said host cell an extract comprising the fusion protein, and

(c) purifying the fusion protein using a chromatography column.

17. (Amended) A method of making a pharmaceutical composition comprising:

(a) expressing in a host cell a DNA encoding a fusion protein, said protein being a polypeptide of claim 8 [fusion of (i) a polypeptide free of toxin activity and capable of inducing protective immunity against a botulinum toxin, and (ii) a purification moiety that binds to a chromatography column],

(b) obtaining from said host cell an extract comprising the fusion protein,

(c) purifying the fusion protein using chromatography column,

(d) incorporating the purified fusion protein into a pharmaceutical composition.

19. (Three Times Amended) A pharmaceutical composition comprising:

(a) a fusion protein, said protein being a fusion of (i) a polypeptide as described in claim [3] 5, and (ii) a polypeptide that binds to a chromatography column; and

(b) a pharmaceutically acceptable carrier.

21. (Three Times Amended) A pharmaceutical composition according to Claim [20] 19 wherein the fusion protein comprises a polypeptide that binds to an affinity chromatography column.

26. (Amended) An isolated fusion protein comprising (1) a sequence of amino acids [corresponding to a fragment or a derivative of a heavy chain of a type F

botulinum neurotoxin, which is (a) free of botulinum toxin activity, (b) is free of toxoid, and (c) elicits, in a mammal, an immunological response that is protective against type F botulinum toxin] selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, and SEQ ID NO:4, and (2) a polypeptide that facilitates or enhances purification of the fusion protein.

28. (Twice Amended) The fusion protein of claim [27] 26 wherein said *C. botulinum* amino acid sequence consists of SEQ ID NO: 1 [the contiguous amino acid sequence of amino acids 848 to 1278 of said *C. botulinum* neurotoxin (SEQ ID NO:1)].

30. (Twice Amended) The fusion protein of claim [27] 26 wherein said [*C. botulinum* neurotoxin] amino acid sequence comprises at least one amino acid sequence selected from SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4 [contiguous amino acid sequence of amino acids 848-991 of said *C. botulinum* neurotoxin (SEQ ID NO:2), the contiguous amino acid sequence of amino acids 992-1135 of said *C. botulinum* neurotoxin (SEQ ID NO:3), or the contiguous amino acid sequence of amino acids 1136-1278 of said *C. botulinum* neurotoxin (SEQ ID NO:4)].

31. (Amended) A composition comprising the fusion protein of claim [27] 26 and [a] diluent, said composition being free of contamination by other clostridial proteins.